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# PLEIOTROPIC EFFECTS OF VITAMIN D: BEYOND BONE HEALTH

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## ABSTRACT

Vitamin $D_3$ (cholecalciferol) is well known for its important role in maintaining calcium balance and bone health. In recent years, it has also been recognized as a molecule with multiple functions in the body. It is produced naturally in the skin when exposed to ultraviolet B (UVB) rays and can also be obtained from food or supplements. After entering the body, it is converted into its active form, 1,25-dihydroxyvitamin $D_3$ (calcitriol), which acts like a hormone. Apart from its classical role in bone metabolism, vitamin $D_3$ has many other effects. It helps regulate immune function, supports cardiovascular and metabolic health, influences brain and nerve functions, and plays a role in cell growth and differentiation. Because of these pleiotropic effects, vitamin $D_3$ may have a role in the prevention and management of several chronic diseases. This review summarizes the various biological actions of vitamin $D_3$, explains how it works at the molecular level, and highlights its clinical relevance and future research possibilities.

## INTRODUCTION

Vitamin D is a fat-soluble compound with well-known roles in calcium balance and skeletal health, but it also functions hormonally, with broad biological effects. Traditionally considered a vitamin, it is an organic compound required in small amounts to support metabolic processes, often acting as a coenzyme or enzyme precursor without providing energy or structural units. It can be obtained from dietary sources or supplements, but endogenous synthesis via skin exposure to ultraviolet B (UVB) radiation accounts for the majority of vitamin D production [1].

Vitamin $D_2$ (ergocalciferol) comes from plant sources such as UV-exposed mushrooms, yeast, and fortified foods [1,2], while vitamin $D_3$ (cholecalciferol), more potent and bioavailable, is

synthesized in the skin from 7-dehydrocholesterol and found in animal-based foods including fatty fish, egg yolk, and fortified dairy products [2,3]. Other forms, such as vitamin $D_4$ (22-dihydroergocalciferol), found in some fungi and vitamin $D_5$ (sitocalciferol), an experimental plant-derived form with potential antioxidant properties are less studied but may have additional biological properties [4,5].

Hormones are chemical messengers that regulate distant target organs, and vitamin D fulfills this role through its active form, 1,25-dihydroxyvitamin D (calcitriol), which is synthesized in the kidney. Calcitriol acts on remote organs such as the intestine, bone, and parathyroid glands by binding nuclear vitamin D receptors (VDRs). This hormonal perspective is reinforced by vitamin D's role in endocrine pathways, neurobiological signaling, and immune modulation [6,7].

Once in the body, vitamin D undergoes metabolic activation. In the liver, it is hydroxylated to form calcidiol (25-hydroxyvitamin D), the major circulating form commonly measured to assess vitamin D status [3,8]. Calcidiol is then converted in the kidney to the biologically active form, calcitriol (1,25-dihydroxyvitamin D), which regulates calcium and phosphate metabolism, promoting intestinal absorption, renal reabsorption, and bone mobilization [9,10].

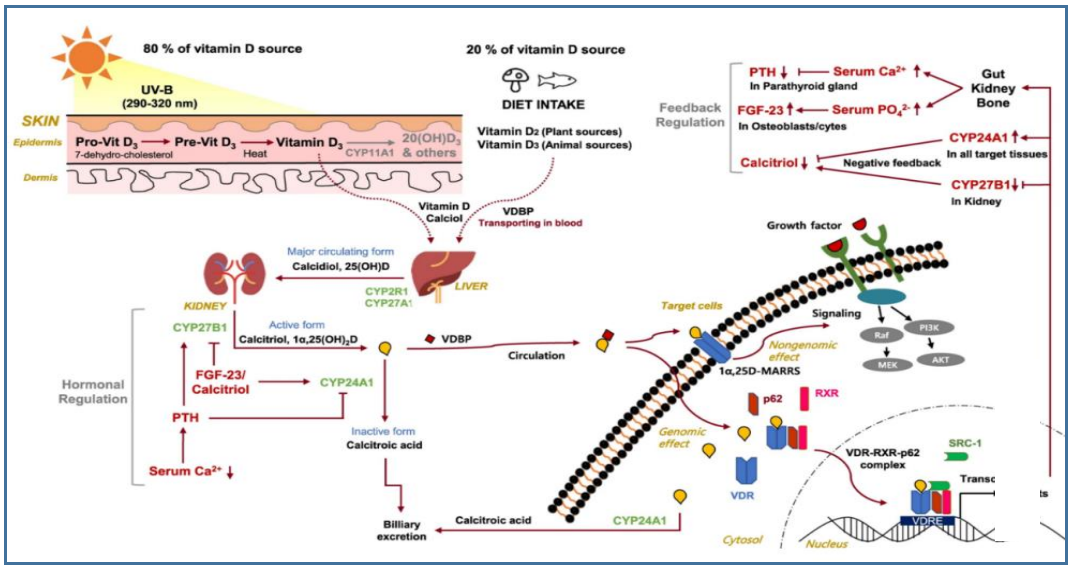


**Fig. 1: Vitamin D Metabolism and Regulation.[12]**

Figure 1 illustrates vitamin D synthesis, metabolism, and regulation. Around 80% of vitamin D is synthesized in the skin from 7-dehydrocholesterol under UVB light, while the remaining 20% is obtained from dietary sources ($D_2$ from plants, $D_3$ from animals). In the liver, vitamin

D is hydroxylated to calcidiol, the main circulating form, and then converted in the kidney to the active hormone, calcitriol. Calcitriol regulates calcium and phosphate homeostasis by acting on the gut, bone, and kidneys. Its levels are tightly controlled by PTH, FGF-23, and serum mineral concentrations, while excess calcitriol is inactivated by CYP24A1 and excreted via bile. This coordinated system ensures vitamin D supports skeletal and extra-skeletal functions.[12]

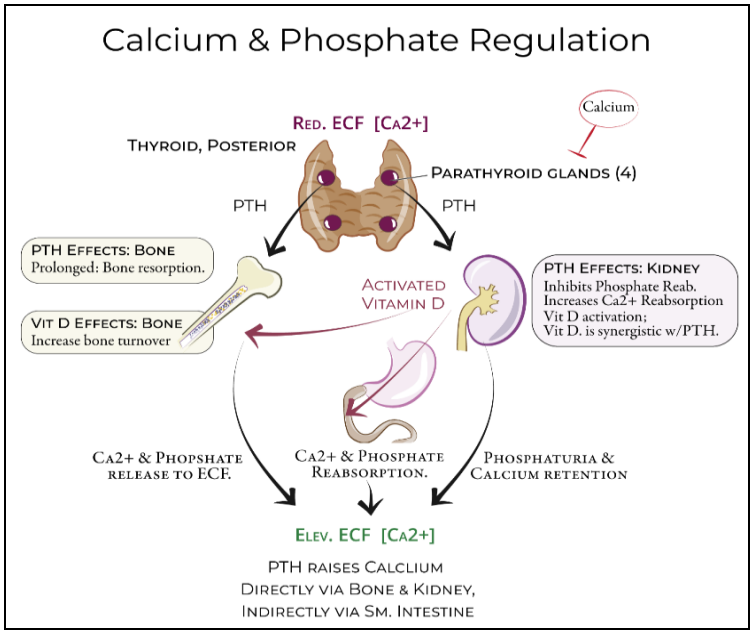


**Fig. 2: Calcium and Phosphate regulation.[13]**

Figure 2 illustrates the integrated regulation of calcium and phosphate homeostasis by parathyroid hormone (PTH) and vitamin D. When extracellular calcium levels drop, the parathyroid glands secrete PTH, which acts on bones to stimulate calcium and phosphate release into the extracellular fluid. In the kidneys, PTH inhibits phosphate reabsorption, enhances calcium reabsorption, and promotes conversion of calcidiol to active vitamin D (calcitriol). Calcitriol acts synergistically with PTH to increase intestinal absorption of calcium and phosphate, contributing to elevated extracellular calcium levels. This coordinated action of PTH and vitamin D maintains calcium and phosphate balance, ensuring proper bone turnover, renal reabsorption, and intestinal absorption.[13]

Beyond its classical roles, vitamin D exerts pleiotropic effects on immune modulation, cardiovascular and metabolic health, neurocognitive function, and cellular growth and differentiation. These diverse actions are increasingly recognized as clinically significant and are the focus of this review.

## Cholecalciferol, Parathyroid Hormone, and Calcitonin in Calcium-Phosphate Homeostasis

Vitamin D, parathyroid hormone (PTH), and calcitonin work together to maintain blood calcium and phosphate levels. Chronic elevation of PTH stimulates osteoclast activity indirectly via osteoblast signaling, resulting in bone resorption and release of calcium and phosphate into the extracellular fluid [14]. In contrast, short, intermittent PTH exposure favors osteoblast-mediated bone formation, increasing bone density [15]. This principle underlies the therapeutic use of intermittent PTH analogs, such as teriparatide, for osteoporosis management [16].

## Pharmacokinetics of Vitamin D

**Absorption and dietary effects:** Being fat-soluble, vitamin D ($D_2$ and $D_3$) absorption depends on bile salts and dietary fat, with improved uptake when taken with meals containing fat. **Distribution and transport:** Circulating vitamin D metabolites bind primarily to vitamin D-binding protein (VDBP) and, to a lesser extent, albumin. Lipophilic cholecalciferol accumulates in adipose tissue, providing a reservoir for sustained release. **Metabolic activation:** Both cholecalciferol ($D_3$) and ergocalciferol ($D_2$) undergo 25-hydroxylation in the liver (CYP2R1, CYP27A1) to produce calcifediol (25[OH]D), followed by renal 1α-hydroxylation (CYP27B1) to form calcitriol ($1,25[OH]_2D$).[17,18,19]

## Half-lives and clinical relevance[1,20,21]

- Calcitriol: 4–6 hours; rapid action, higher hypercalcemia risk
- Calcifediol: ~2–3 weeks; best biomarker for vitamin D status
- Cholecalciferol: stored in adipose tissue; slow, sustained release

## Special populations

Patients with fat-malabsorption or renal failure may require calcifediol or active vitamin D analogs due to impaired absorption or hydroxylation.[22]

## Vitamin D and Hypertension

Vitamin D influences blood pressure partly by modulating the renin-angiotensin system (RAS) and intracellular calcium in vascular smooth muscle. Animal and human studies suggest that vitamin D deficiency is associated with increased renin activity and hypertension, while supplementation can inhibit RAS and improve vascular function [23,24].

Beyond RAS, vitamin D also impacts vascular endothelium, smooth muscle contractility, nitric oxide pathways, oxidative stress, and prostacyclin production, all contributing to blood pressure regulation [25]. Additionally, vitamin D exerts anti-inflammatory effects that may reduce vascular inflammation, a key factor in endothelial dysfunction and hypertension. It also modulates parathyroid hormone and phosphate balance, indirectly influencing vascular stiffness and arterial compliance. Observational studies have linked low serum 25-hydroxyvitamin D levels with higher risk of both systolic and diastolic hypertension, particularly in populations with obesity, metabolic syndrome, or chronic kidney disease. However, meta-analyses generally support beneficial effects of vitamin D supplementation on blood pressure, showing modest but significant reductions, particularly in hypertensive populations or when higher doses are used [26], suggesting that baseline vitamin D status, dose, duration, and comorbidities may influence the antihypertensive response.

**Vitamin D and Alzheimer's Disease**

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline. Emerging evidence links low serum vitamin D to an increased risk of AD and dementia [27]. Vitamin D receptors (VDRs) are widely expressed in the brain, and the active form of vitamin D regulates neurotrophin expression, supports neural cell survival, and modulates neurite growth, neurotransmission, synaptic plasticity, and amyloid plaque clearance [28]. In vitro studies further show that vitamin D can reduce amyloid-induced cytotoxicity, apoptosis, and inflammatory responses in cortical neurons, suggesting a neuroprotective role [29].

While conventional AD treatments (donepezil, rivastigmine, galantamine, memantine) remain symptomatic, vitamin D shows promise as a multitargeted adjunct therapy. Observational studies indicate that higher dietary vitamin D intake is associated with a lower risk of developing AD [30].

Clinical trials suggest potential benefits when vitamin D is combined with other agents, such as memantine or DHA, in slowing cognitive decline and enhancing neuroprotective effects compared to monotherapy [31].

**Vitamin D and Diabetes Mellitus (DM)**

Vitamin D plays a crucial role in glucose metabolism and diabetes. Its active form, 1,25-dihydroxyvitamin $D_3$, enhances pancreatic β-cell function, promotes insulin secretion, and

supports β-cell survival [32]. It also improves peripheral insulin sensitivity by modulating insulin receptor expression and glucose transporter activity, while deficiency has been linked to insulin resistance and impaired glucose tolerance [33]. Additionally, vitamin D exhibits anti-inflammatory effects by downregulating cytokines such as TNF-α and IL-6, which contribute to insulin resistance and β-cell dysfunction. Observational studies suggest adequate vitamin D intake, particularly during early life, may reduce autoimmune β-cell destruction, lowering the risk of type 1 diabetes [34]. In type 2 diabetes, vitamin D supplementation has been associated with improvements in glycemic control, including reductions in fasting glucose and enhanced insulin sensitivity, although outcomes are variable across studies [35]. These effects, combined with its anti-inflammatory and immunomodulatory properties, highlight vitamin D's pleiotropic role in the prevention and management of diabetes.

**Role of Vitamin D in Brain Function and Stroke**

Emerging evidence suggests that vitamin D may play a significant role in the context of ischemic stroke. Low serum vitamin D levels have been reported more frequently in patients with ischemic stroke compared to those with hemorrhagic stroke, though current studies remain limited and inconclusive [36]. Deficiency of vitamin D has also been associated with greater stroke severity, poorer prognosis, and less favorable clinical outcomes. The neuroprotective effects of vitamin D are thought to involve multiple mechanisms, although these are not yet fully elucidated. Vitamin D may help maintain the integrity of the blood–brain barrier (BBB), support endothelial function, and regulate molecular transport within the central nervous system. In ischemic stroke, BBB dysfunction arises due to excessive reactive oxygen species (ROS) generation, nitric oxide imbalance, intracellular calcium dysregulation, and increased vascular endothelial growth factor (VEGF) expression, all contributing to neuronal injury. By modulating these pathways, vitamin D could potentially mitigate neuronal damage and support neurorecovery[37].

**Role of Vitamin D in Psoriasis**

Psoriasis is a chronic immune-mediated skin disease affecting about 2%–3% of the population, characterized by excessive keratinocyte growth, impaired skin barrier, and infiltration of inflammatory cells [38]. The epidermis is the natural site of vitamin D production through ultraviolet B (UVB) exposure, and vitamin D is now recognized as an important regulator of skin immunity and inflammation [39]. Its precursor, 7-

dehydrocholesterol, is present in the basal and spinous layers of the epidermis, where it is converted to the active form, calcitriol.

Calcitriol binds to vitamin D receptors (VDRs) in keratinocytes to control their proliferation, differentiation, and apoptosis. It reduces inflammatory markers such as S100A7 and regulates keratin synthesis (K1, K10), involucrin, loricrin, filaggrin, and glycosylceramides, supporting barrier integrity [40]. These effects involve both genomic mechanisms through VDR-mediated gene transcription and non-genomic pathways, including regulation of intracellular calcium via calcium receptors and phospholipase C enzymes [41]. Vitamin D deficiency or VDR dysfunction disrupts epidermal differentiation, leading to basal layer hyperproliferation and impaired barrier function.

Clinically, topical vitamin D analogs such as calcipotriol, calcitriol, tacalcitol, and maxacalcitol are widely used to treat localized plaque psoriasis, alone or with corticosteroids. Their benefits include reducing keratinocyte proliferation, promoting differentiation, and suppressing inflammatory cytokines (IL-2, IL-6, IFN-γ) and antimicrobial peptides in psoriatic lesions.[42].

**Role of Vitamin D in Community-Acquired Pneumonia (CAP)**

Vitamin D is increasingly recognized for its protective role against respiratory infections, including pneumonia. The active form of vitamin D induces the expression of antimicrobial peptides such as cathelicidin and defensins in respiratory epithelial cells, enhancing innate immunity and microbial clearance [43]. Vitamin D also modulates adaptive immune responses, suppressing excessive pro-inflammatory cytokine production while promoting regulatory T-cell activity, which can reduce lung tissue damage during infection [8]. Observational studies have linked low serum 25-hydroxyvitamin D levels with increased susceptibility to community-acquired pneumonia, higher severity of illness, and poorer outcomes [44]. Randomized controlled trials suggest that vitamin D supplementation, particularly in individuals with deficiency, can reduce the risk of acute respiratory infections, supporting its potential as an adjunctive preventive strategy [45,46].

**Role of Vitamin D in cancer**

Vitamin D has emerged as a potential modulator of cancer risk and progression through its regulatory effects on cell proliferation, differentiation, apoptosis, and immune surveillance. The active form, 1,25-dihydroxyvitamin D (calcitriol), binds to vitamin D receptors (VDR)

and modulates the transcription of multiple genes involved in cell cycle control, thereby inhibiting tumor initiation, growth, and metastasis[47]. Experimental studies demonstrate that calcitriol can suppress angiogenesis, downregulate pro-inflammatory signaling, enhance DNA repair, and strengthen antitumor immune responses[48]. Epidemiological data consistently link low serum vitamin D levels to an increased risk of breast, colorectal, and prostate cancers, with observational studies suggesting a protective effect of higher vitamin D status or supplementation [49,50]. While randomized controlled trials are still limited, vitamin D shows promise as a multitargeted adjunct in cancer prevention and therapy. Development of selective vitamin D analogs with minimal calcemic effects may further enhance its therapeutic utility in oncology.

## CONCLUSION

Vitamin D, once known mainly for its role in calcium–phosphate balance and bone health, is now recognized as a pleiotropic hormone with wide-ranging effects on many organ systems. Through its genomic and non-genomic actions, vitamin D influences immune modulation, cardiovascular function, metabolism, cancer progression, and brain health. Its deficiency has been associated with an increased risk of several acute and chronic diseases, emphasizing its importance in maintaining overall health and resilience. The pleiotropic nature of vitamin D highlights its potential as an immunomodulatory and regulatory molecule rather than merely a nutrient. Future research should focus on defining optimal vitamin D levels, understanding its role in extra-skeletal diseases, and exploring its therapeutic applications to improve prevention and clinical outcomes.

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